

WHAT IS CLAIMED IS:

1. A hydrolytically stable, biologically active conjugate that is the reaction product of a biologically active molecule having a reactive thiol moiety and a water-soluble polymer having an active ethyl sulfone moiety having a reactive site located at the second carbon from the sulfone group and wherein said sulfone moiety forms a linkage with said reactive thiol moiety of said biologically active molecule to form said conjugate.
2. The conjugate of Claim 1 wherein said biologically active molecule is a protein and said reactive thiol moiety is contained within a cysteine moiety of said protein.
3. The conjugate of Claim 1 wherein said water soluble polymer is selected from the group consisting of poly(alkylene oxides), poly(oxyethylated polyols), and poly(olefinic alcohols).
4. The conjugate of Claim 1 wherein said water soluble polymer includes a second active moiety, which may be the same or different from said active sulfone moiety, and wherein said second active moiety forms a linkage with a second biologically active molecule.
5. The conjugate of Claim 1 wherein said biologically active moiety is selected from the group consisting of proteins, pharmaceuticals, cells, vitamins, and combinations thereof.
6. The conjugate of Claim 1 wherein said ethyl sulfone moiety is a haloethyl sulfone.
7. The conjugate of Claim 1 wherein said water soluble polymer is poly(ethylene glycol).
8. A biologically active conjugate that is the reaction product of an activated water soluble polymer having at least one active ethyl sulfone moiety that is selective for reaction with thiol moieties and at least one other moiety that is selective for reaction

with amino moieties; a first protein having a thiol moiety wherein said thiol moiety forms a hydrolytically stable linkage with said ethyl sulfone moiety on said polymer; and a second protein having an amino moiety wherein said amino moiety forms a linkage with said other moiety on said polymer.

9. The conjugate of Claim 8 wherein said first protein contains cysteine units and said second protein contains lysine units.

10. The conjugate of Claim 8 wherein said water soluble polymer is selected from the group consisting of poly(alkylene oxides), poly(oxyethylated polyols), and poly(olefinic alcohols).

11. The conjugate of Claim 8 wherein said conjugate is a dumbbell structure.

12. A hydrolytically stable biologically active conjugate that is the reaction product of biologically active molecules, each having a reactive thiol moiety, and a water soluble polymer having at least two active ethyl sulfone moieties, each active ethyl sulfone moiety having a reactive site located at the second carbon from the sulfone group and wherein said sulfone moieties form a linkage with said reactive thiol moieties of said biologically active molecules to form said conjugate.

13. A method for synthesizing a water soluble activated organic polymer having an active ethyl sulfone moiety wherein the linkage between the polymer and the active ethyl sulfone moiety is stable against hydrolysis, the method comprising the steps of linking a sulfur containing moiety directly to a carbon atom of the polymer and then converting the sulfur containing moiety to an active ethyl sulfone moiety.

14. The method of Claim 13 further comprising the step of isolating the activated polymer having the active ethyl sulfone moiety.

15. The method of Claim 13 wherein said step of linking a sulfur containing moiety directly to a carbon atom of the polymer comprises the steps of activating at least one activatable hydroxyl moiety on the polymer and reacting the resulting compound

with an alcohol containing a thiol moiety to cause sulfur to be linked directly to the carbon-carbon chain of the polymer.

16. The method of Claim 15 wherein said step of activating at least one activatable hydroxyl moiety is selected from the steps consisting of hydroxyl substitution and replacement of hydroxyl hydrogen with a more reactive moiety.

17. The method of Claim 15 wherein the alcohol containing the thiol moiety is converted to an active ethyl sulfone moiety by the steps of oxidizing the sulfur in the sulfur containing moiety to ethyl sulfone.

18. A method for preparing an activated poly(ethylene glycol) ethyl vinyl sulfone comprising the steps of:

(a) reacting poly(ethylene glycol) having at least one active hydroxyl moiety with a compound to form either an ester or a halide substituted poly(ethylene glycol);

(b) reacting the ester or a halide substituted poly(ethylene glycol) of step (a) with mercaptoethanol to substitute the mercaptoethanol radical for the ester or halide moiety;

(c) reacting the mercaptoethanol substituted poly(ethylene glycol) of step (b) with an oxidizing agent to oxidize sulfur in the mercaptoethanol moiety to sulfone; and

(d) reacting the ethyl sulfone of step (c) with a compound to convert the hydroxyl of the mercaptoethanol moiety to an ester or halide moiety to form an activated ethyl sulfone.

19. A method for preparing a conjugate of a substance and a water soluble activated polymer selected from the group consisting of poly(alkylene oxides), poly(oxyethylated polyols), and poly(olefinic alcohols) having at least one ethyl sulfone moiety, said method comprising the steps of reacting the substance with the activated

polymer having an active ethyl sulfone moiety and forming a linkage between the substance and the polymer derivative.

20. The method of Claim 19 wherein the substance includes an active thiol moiety and the linkage is between the thiol moiety and the sulfone moiety.

21. The method of Claim 19 wherein the substance includes an active amino moiety, the polymer derivative includes an amino-selective moiety, and a linkage is formed between the amino moiety and the amino selective moiety.